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10/567,025	08/16/2006	Yixin Wang	VDX5006USPCT	5348

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EXAMINER	
BAUSCH, SARAE L	

ART UNIT	PAPER NUMBER
1634	

NOTIFICATION DATE	DELIVERY MODE
04/16/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/567,025	WANG ET AL.	
	Examiner	Art Unit	
	SARAE BAUSCH	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56,65-92,101-129 and 137-221* is/are pending in the application.

4a) Of the above claim(s) *2,4,5,36-56,65-72,74,76,77,107-129 and 137-221* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6-35,73,75,78-92 and 101-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of group I and the combination of L1CAM and PLAB in the reply filed on 06/26/2009 is acknowledged.

2. Claims 2,4,5,35-56,65-72,74,76,77,107-129 and 137-221 withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 06/26/2009.

3. Claims 1, 3, 6-34, 73, 75, 78-92, and 101-106 are under examination of the elected gene combination of L1CAM and PLAB, SEQ ID NO 1 and 2. Additionally PCR products, SEQ ID NO 25 and 26 are under examination for claim 22. It is noted the claims 1-20, 29-32, 37-56, 65-70, 73-92, 101-106, 109-129, and 137-142 linked the inventions of group I and II and the claims that read on the elected gene combination of L1CAM and PLAB are under examination.

Claim Rejections - 35 USC § 112- 2nd Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 11-18 and 83-90 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 11 and 83 recites the limitation "the specificity" and "the sensitivity" in lines 1-2 of claim 11 and 83. There is insufficient antecedent basis for this limitation in the claim. Claim

11 depends from claim 1 however claim 1 does not require determining specificity or sensitivity in the method.

Claim Rejections - 35 USC § 112- 1st Paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 3, 6-34, 73, 75, 78-92, and 101-106 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims

The claims are drawn to methods for identifying a melanoma and distinguishing a malignant melanocyte from a benign melanocyte in a tissue sample by measuring the expression level of PLAB and L1CAM wherein the expression level above pre-determined cut-off levels indicate the presence of melanoma in a sample. Additional claims further limit the melanoma to micro metastasis and limit specificity and sensitivity to detect metastasis as well as limit the pre-determined cut-off level to be at least two fold over-expression.

Dependent claims are limited to a sample that is a lymph node, obtained from a biopsy or inter-operatively and gene expression measured on a microarray or by PCR and PCR product detected is SEQ ID NO 25-26. Additional dependent claims comprise measuring expression of a gene constitutively expressed in the sample, reducing melanin in a sample and extracting RNA from a sample.

The claims encompass analysis of any human or non-human subject and any type of sample. The claims encompass using L1CAM and PLAB in any manner with a pre-determined cut-off value which includes analysis of any level of gene expression, any sample, any comparison to any control or any undisclosed pre-determined cut-off value for the diagnosis of melanoma, including micro metastasis and metastasis.

The nature of the claimed invention thus requires knowledge of a robust and reliable correlation between gene expression levels in different sample types from both human and non-human and the presence of melanoma to determine diagnosis, as well the ability to determine the stage and severity of melanoma including metastatic melanoma, as well as determine benign melanocyte, or normal tissue based on the expression levels of PLAB and L1CAM.

Guidance in the Specification and Working Examples

The specification teaches analysis of gene expression of malignant melanoma, benign skin nevi, and normal skin tissues to determine differentially expression genes in malignant melanoma. The specification teaches analysis of RT-PCR analysis of PLAB and L1CAM in samples of malignant melanoma, benign nevi, melanoma LN metastasis, and melanoma-free lymph node samples (see pg. 3-4). The specification teaches analysis of melanoma and benign nevi primary tissue for microarray analysis including 45 primary malignant melanoma, 18 benign skin nevi, and 7 normal ski tissues in addition to analysis of 77 malignant melanoma LN metastasis and 18 melanoma-free LN samples for PCR analysis. The specification provides expression analysis and identified genes with a $p<.05$ and fold change of at least 2 (see pg. 32) and teaches that L1CAM and PLAB had a greater than 10 fold change between melanoma, benign nevi and normal skin samples (See table 9). Analysis was then determined in primary melanoma and melanoma LN metastasis, benign melanocytes, and normal samples by RT-PCR of L1CAM and PLAB (see ex 7).

None of the examples in the specification teach analysis of diagnosing an individual with having or not having melanoma, or demonstrating the ability to distinguished based on expression analysis the different stages of melanoma. The specification merely provides a study to determine L1CAM and PLAB are markers genes indicating increased risk of melanoma. The specification does not provide for the analysis of any type of control sample other than benign nevi or normal skin nor does analysis in any other type of subject other than human, the specification merely demonstrate L1CAM and PLAB are associated with increased risk of

melanoma. The specification does not teach a representative number of species analysis of melanoma associated expression analysis of L1CAM and PLAB (cat, dog, horse, cow, etc).

The specification does not teach nor provide guidance that amount of expression level necessary that will be predictive of diagnosis or stage of melanoma in any human or non-human. The specification does not provide guidance that any amount of increase or decrease based on any predetermined cut off value will be predictive of diagnosis and staging of melanoma, as predictably association expression level to diagnosis or staging of a disease is highly unpredictably.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to determining the level of any particular transcription product is high, the unpredictability associated with correlating any compared level with a particular phenotype such as identifying melanoma or metastasis of melanoma is even higher. Such unpredictability is demonstrated by the prior art, the post-filing art, and the instant specification.

The claims encompass the use of any amount of an increase or decrease in level of gene expression of PLAB and L1CAM as compared to any control of a pre-determined cut off value for the diagnosis and determination of metastasis of melanoma in any sample from human or non-human subjects, however the prior art teaches that determination of diagnosis of melanoma and metastasis of melanoma based on expression analysis is unpredictable.

McMasters (2003, cited on IDS), teaches that RT-PCR analysis may be useful tool for staging of melanoma but that there are many limitations and a diagnostic test must be sensitive

but have greater specificity (see pg. 336). McMasters warns that several important issues remain to be resolved before RT-PCR analysis can be used for clinical decision making including standardization and optimization of techniques and includes the best combination of markers to obtain optimal balance between sensitivity and specificity, which has yet to be defined (see pg. 337). The specification does not provide any guidance that the markers of PLAB and L1CAM are specific.

Additionally, the art teaches that gene expression analysis is commonly used for three different purposes: (1) as a screening tool to identify individual genes of interest that might contribute to an important biological function, (2) to obtain insight into an important biological function, and (3) as a classification tool to sort cases into clinically important categories (Pusztai and Hess, Annals of Oncology, Vol. 15, pages 1731-1737, 2004; e.g., paragraph bridging pages 1732-1733). In the instant case, the specification uses gene expression analysis to determine a PLAB and L1CAM are associated with an increased risk of melanoma, however the claims are drawn to using gene expression analysis to diagnose and determine the stage of melanoma. The specification does not teach that the analysis of expression of the genes L1CAM or PLAB will diagnosis or determine the severity of melanoma. The specification merely provides an analysis of expression levels in samples obtained from patients already diagnosed with melanoma, however the claims are drawn to diagnosis and determining of staging and the specification does not provide guidance how to classify a subject as having melanoma or determine the stage of melanoma in any human or non-human subject. Pusztai and Hess teach that validation of gene expression important to biological function may be validated by using different methods, such as RT-PCR, whereas the most appropriate validation for using gene expression analysis as a

classification tool is testing the predictor on independent sets of cases (e.g., page 1733, left column, 1st full paragraph). In the instant case the specification does not test L1CAM and PLAB on independent sets of cases. However post filing art does evaluate the marker L1CAM and PLAB on independent sets of cases and is unable to identify melanoma by expression of L1CAM and PLAB.

The prior art reveals that differences in gene expression observed between two groups do not necessarily provide markers that can be used to reliably classify a subject and thus diagnosis melanoma or determine metastasis of melanoma. Golub et al (Science, Vol. 286, pages 531-537, October 1999) teach the use of a two-step procedure to test the validity of gene expression levels as predictors: step 1 involves cross-validation of the predictors on the initial data set, where one withholds a samples, builds a predictor based only on the remaining samples and predicts the class of the withheld sample; step 2 involves the repetition of assessing the clinical accuracy of the predictor set on an independent set of samples (e.g., page 532, right column). Although Golub et al could detect gene expression differences between chemotherapy responders and non-responders, those differences could not be use to predictably classify individuals (e.g., page 533, paragraph bridging left and middle columns). Accordingly, the art demonstrates the unpredictable nature of extrapolating gene expression differences to a method of class prediction.

Additionally, post filing art could not predictably identify melanoma by expression analysis of L1CAM and PLAB. Hilari et al. (Ann Surg Oncol (2009), 16:177-185) teach evaluating prognostic potential of qRT-PCR in melanoma patients using specific markers. Hilari teaches PLAB and L1CAM were evaluated for melanoma specificity but not for sentinel lymph node analysis. Hilari teaches that PLAB and L1CAM did not differentiate between malignant

melanoma and benign melanocytes or lymph nodes in their analysis and conclude that LAB and L1CAM are not possible markers for melanoma metastasis to SLNs (see abstract). Hilari teaches using applicants own primers and probes for L1CAM and PLAB and evaluating a set of benign nodes, positive nodes, RNA from melanocytes, and RNA from ski. Hilari demonstrates that no discriminatory power between benign versus positive nodes or between benign nevi/normal skin versus positive nodes using the markers L1CAM and PLAB(see pg. 180 and figure 2) and thus concludes that these markers are not useful for staging of melanoma SLNs. The teaching of Hilari demonstrate the unpredictability of reproducing expression analysis data in different data sets with the ability to classify an individual as having melanoma or determining stage of melanoma.

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the claimed invention. Given the lack of guidance in the specification, one would have to perform large case: control analyses to determine PLAB and L1CAM expression levels, as compared to any control level in any type of sample, is in fact diagnostic and predictive of staging of melanoma as recited in the claims, which would include validation studies. Such experimentation would be required for any control sample in any species, human or non-human, as encompassed by the claims. Even if such experimentation were to be performed, there is no assurance that the association asserted in the specification would be repeated and shown to be robust and reliable as demonstrated by Hilari.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the particular examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention.

Conclusion

8. No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sarae Bausch whose telephone number is (571) 272-2912. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

/Sarae Bausch/
Primary Examiner, Art Unit 1634